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Analyses of Prognostic Factors in a Retrospective Review of 92 Children With Ependymoma: Italian Pediatric Neuro-Oncology Group

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The principal aim of this report is to present the results of multivariate analyses conducted to identify clinical prognostic factors in 92 children aged <16 years with ependymoma (EPD) retrospectively collected in seven Italian centres. They were treated over a 16-year period (1977–1993). Treatment modalities varied. Surgery and radiotherapy (RT) was the ''gold standard'' management method for the majority of these children. Only in the late 1980s did some of them receive chemotherapy (CT), mainly with vincristine, lomustine (CCNU) and prednisone. The median follow-up of the entire study population is 36 months (average 43 months; range 12 to 214 months). The 10-year overall (OS) and the progression-free survival (PFS) of the study population were 55.5% (CI 41.4–69.4%) and 34.7% (CI 21.4–47.8%), respectively. Age (<5 years; >5 years), sex, site (infratentorial vs. supratentorial), histology (anaplastic/malignant vs. non-anaplastic/non-malignant), type of resection (complete vs. incomplete); use and fields of RT, and of CT employed were entered in a multivariate regression model to test their impact on OS and PFS. On univariate analysis, radical surgery, the use of RT and age more than 5 years at the time of diagnosis achieved statistically significant values for predicting long-term OS and PFS. Histology reached marginal statistical significance but only for PFS. When those variables were entered in a multivariate analysis only radical resection ($P = 0.00142$ and 0.0001) resulted a significant factor for predicting long-term OS and PFS, while the use of RT reached a marginal statistical significance, but only for PFS ($P = 0.05$). Children who had the tumour completely resected did significantly better than all the others who had less than a complete resection, with a 10-year OS and PFS for the two groups of patients of 69.8% (CI 53–86.5%) and 57.2% (CI 40.3–75%) and of 32.5% (CI 8.5–57.6%) and 11.1% (0–24.4%), respectively. These findings suggest that, for childhood EPD, radical resection should be pursued as much as reasonably possible. Thus, it seems justified proposing for future trials, patient stratification by entity of surgical resection. Med. Pediatr. Oncol. 29:79–85, 1997.

Key words: ependymoma; brain tumours; prognostic factors

INTRODUCTION

Controversies still exist concerning the optimal management of childhood ependymoma (EPD). Historically, EPD were treated according to medulloblastoma protocols, assuming similarity of biological and clinical behaviour [1]. It has been only recently that the validity of this assumption has been firmly denied, as knowledge of the biological and clinical peculiarities of EPD increased. Consequently, there has developed a real need for targeted research concerning EPD and its management. This need is accentuated when two points are considered. First, children affected by EPD seem to have quite remarkable prognostic disparities. It is, however, still difficult to predict precisely on the basis of clinical indices what will be the outcome of therapy given to each child affected by this tumour. Second, due to increased con-

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cern regarding the late effects of treatments given to children affected by central nervous system (CNS) tumours, it has become a top priority to modulate therapeutic aggressiveness carefully in order to achieve acceptable cost-benefit ratio. The definition of well-defined prognostic factors is essential if these goals are to be achieved. This review was undertaken with these needs in mind. We here present the results of analyses of prognostic factors identified in a large population of Italian children with intracranial EPD.

MATERIALS AND METHODS

The present report is based on 92 children with EPD treated between 1977 and 1993. They were collected as part of an Italian retrospective cooperative study comprising the Neurologic Institute ''Carlo Besta'' in Milan, the Tumour Institute in Milan, the Neurosurgical Divisions of Bologna (O.C. Bellaria), Verona, the Paediatric Neuro-Oncology Programs of the Department of Paediatrics of the University of Padova, Torino, and of the Hospital ''Giannina Gaslini'' in Genova. Specific data collection forms and detailed instructions were given to the physicians in charge of the study at each institution. Information was gathered only on children aged less than 16 years with an histologically proven intracranial EPD and for whom detailed information on the initial original treatment was available. EPD defined by the contributing peripheral centre as ''anaplastic, malignant or Grade III and IV'' were considered ''malignant/anaplastic'' while all the others, ''EPD nos (not otherwise specified) or grade I and II,'' were considered ''non-malignant/non-anaplastic.'' The patients affected by spinal EDP or by brain tumours designed as ependymoblastoma were excluded.

The completeness of the surgical resection was judged according to the neurosurgical notes and the neuroradiological findings, whenever available, if performed within a month after surgery. If discordance was noted, more information was requested from the participating institution. If discordance remained, surgery was codified as incomplete. All resections defined as subtotal, partial or biopsy only were considered non-radical. Treatment modalities varied, but surgery and radiotherapy (RT) was used for the majority of these children. Only in the late 1980s did some of them receive chemotherapy (CT), mainly with vincristine, lomustine (CCNU) and prednisone.

Survival curves were calculated according to the Kaplan-Meier method [2]. The overall survival (OS) curve as calculated considering the time interval between the date of diagnosis and the date of last follow-up or death. For the progression-free survival (PFS) curves, the interval between diagnosis and the last follow-up or the date of relapse or progression was considered. Cox regression models for dependent variables and Forward Stepwise Sequence of Chi-squares for the Log rank test were applied for prognostic factors analyses [3,4]. Furthermore, the standard error estimates of Peto were also used to correct possible differences derived by the different follow-up of some subgroups of children of this study population [4]. Age groups (less or more than 5 years), sex, tumour site (infratentorial vs. supratentorial), histology (non-malignant/non-anaplastic vs. malignant/anaplastic), surgery (complete resection vs. incomplete resection), use of RT, field of RT (regional/local vs. craniospinal) and use of CT were the clinical characteristics entered in the univariate analysis; those variables found to be significant at the 0.1 level were introduced in a multivariate analysis.

RESULTS

Clinical Characteristics

The age range of the study population varied between 3 and 162 months with a mean and a median of 72 and 63 months, respectively. The ages of the groups of children considered by primary site (infratentorial vs. supratentorial) and histology (non-malignant/non-anaplastic versus malignant/anaplastic) were similar to the one of the whole study population. The other main clinical characteristics of the group of patients as a whole and then when divided by primary site (infratentorial vs. supratentorial), histology (malignant/anaplastic vs. non-malignant/non-anaplastic) and age groups, are reported in Table 1. Our data reflect quite closely the clinical characteristics of similar cohorts of patients reported by others [5–8]. Sixty-five percent of the tumours occurred in the posterior fossa, and about a third were ''anaplastic/malignant.'' This latter histologic variety of EPD was equally distributed between sites (infra- and supratentorial) and age groups. Two of 29 children (7%) who were staged with myelography or contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the spine showed evidence of tumour dissemination at presentation. They occurred, respectively, in two children with posterior fossa EPD as defined as ''non-malignant/non-anaplastic'' in one and ''malignant/anaplastic'' in the other. One of them was under 2 years of age at diagnosis.

Treatment Results

Detailed information on the entity of radical resection is available on 88 patients; 53 of them (60%) had the tumour completely resected (Table I). The complete resection rates did not differ by primary site, histology and age group. Sixty-four percent of those who had the tumour completely resected are alive with no evidence of disease (NED) while only 5 (14%) of the 35 who did not

TABLE I. Clinical Characteristics of the Study Population

				Site infratentorial		Site supratentorial		Nonmalignant non-anaplastic		Malignant anaplastic		Age <3 (yr)	Age 3–5 (yr)	Age >5 (yr)
		no. pts. 92	%	no. pts. 60	%	no. pts. 32	%	no. pts. 61	%	no. pts. 31	%	pts. 27	pts. 17	pts. 48
Sex	female	40	43	23	38	17	53	28	46	12	39	13	9	18
	male	52	57	37	62	15	47	33	54	19	61	14	8	30
Site	infratentorial	60	65	—		—	—	39	64	21	68	22	8	30
	supratentorial	32	35	—		—	—	22	36	10	32	5	9	18
Histology	non-malignant/non-anaplastic	61	66	39	65	22	69					16	6	39
	malignant/anaplastic	31	34	21	35	10	31					11	11	9
Surgical resection	complete	53	58	35	58	18	56	38	62	15	48	15	4	34
	incomplete	35	38	23	38	12	37	20	33	15	48	10	13	12
	not known	4	—	2	—	2	—	3		1		2	0	2
Radiotherapy	yes	74	80	50	83	24	75	53	87	21	68	17	16	41
	not	16	17	10	17	6	19	6	10	10	32	8	1	7
	not known	2	—	—		2		2		—		2	—	—
Chemotherapy	yes	37	40	34	57	3	9	25	41	12	38	11	2	24
	not	48	60	25	42	23	72	32	52	16	52	13	13	22
	not known	7		1		6		4	—	3	—	3	2	2

have complete resection are alive NED. The median follow-up of the patients alive NED is 37 months, with a median of 51 months and a range varying between 10 and 204 months. More than 80% of the children were irradiated after surgery; information on the RT fields used is reported in Table II. The RT fields used divided equally between the craniospinal and the loco/regional field. No different distribution of those two types of RT fields was noted by primary tumour site and histology. All but four received RT doses >45 Gy to the primary tumour site.

The median follow-up of the whole study population is 36 months (average 43 months; range 12 and 214 months). The 10-year OS and PFS of the 92 children of this series resulted 55.5% (41.4–69.4%) and 34.7% (21.4–47.8%), respectively (Fig. 1). Forty-six children progressed or relapsed; 37 had a local component of the recurrence (80%). The median time to tumour progression or relapse is 17 months (mean: 22 months, range 4 and 84 months).

Prognostic Factor Analyses

The end point for the prognostic factors analyses were the 10-year OS and PFS. As reported in Table III, on univariate analysis ''complete resection,'' the use of RT and age more than 5 years at the time of diagnosis achieved statistical significance for predicting long OS and PFS. Histology reached marginal significance but only for PFS. When those variables were entered in a multivariate analysis, only ''complete resection'' remained a significant factor for predicting long-term OS and PFS ($P = 0.00142$ and 0.0001). Children who had the tumour completely resected did significantly better than all the others who had less than a ''complete resection,'' with a 10-year OS and PFS for the two groups of patients of 69.8% (CI 53.0–86.5%) and 57.2% (CI 40.3–75.0%) and of 32.5% (CI 8.5–57.6%) and 11.1% (0–24.4%), respectively (Fig. 2a, b). These differences were

TABLE II. Radiotherapy Fields Used for the 74 Children Who Were Irradiated

	No. pts.	Craniospinal field	Local/regional field
Infratentorial ependymoma	50	24 (48%)	26 (52%)
Non-malignant/non-anaplastic	36	16	20
Malignant/anaplastic	14	8	6
Supratentorial ependymoma	24	13 (54%)	11 (46%)
Non-malignant/non-anaplastic	17	10	7
Malignant/anaplastic	7	3	4
Total	74	37	37

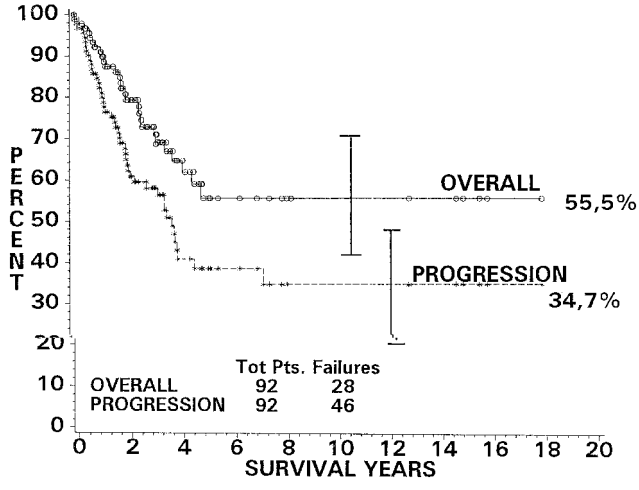

Fig. 1. Ependymomas. Overall and progression-free survival.

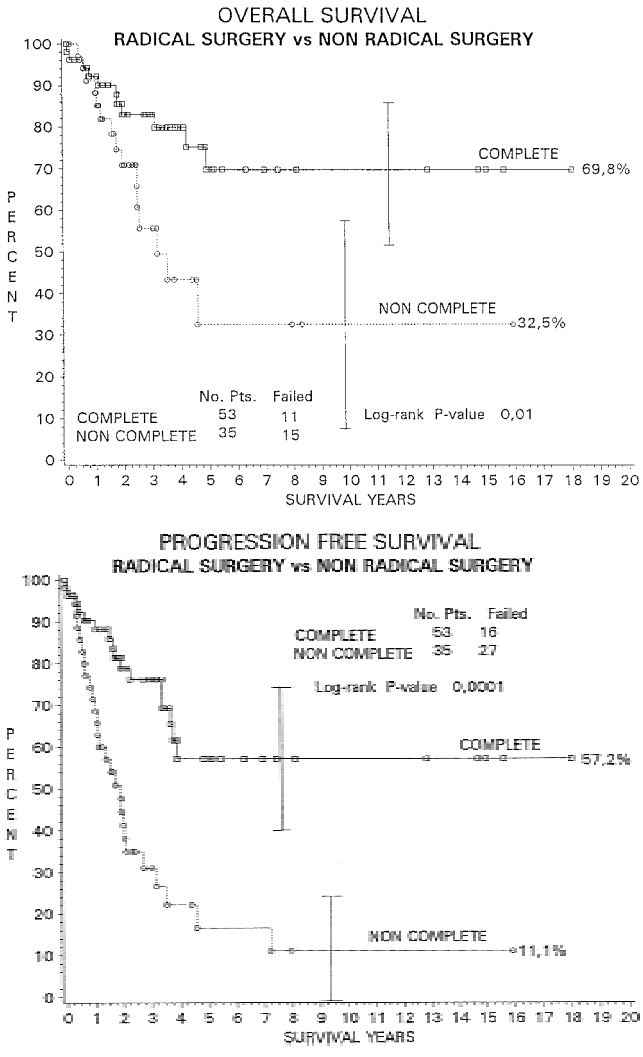

Fig. 2. **a:** Overall survival. Radical surgery vs. nonradical surgery. **b:** Progression-free survival. Radical surgery vs. nonradical surgery.

statistically significant. RT reached only a marginal statistical significance value but only for PFS (= 0.05); the 10-year OS of the irradiated and the nonirradiated group was 58.4% (CI 43.5–73.4%) and 52.0% (CI 24.3–80.2%) and the 10-year PFS 41.2% (CI 23.7–52.7%) and 20% (0–50.2%), respectively.

DISCUSSION

EPD are rare tumours accounting for 6% to 12% of all CNS neoplasm [9]. Almost half of the cases occur in children younger than 5 years of age with 20% to 40% of them affecting children less than 2 years. Ninety percent of childhood EPD arise in the brain with more than 60% of the cases in the posterior fossa, while the remaining affect the spinal cord. Due to their rarity and the lack of awareness on their biological characteristics, EPD have escaped attempts of large cooperative prospective trials. In fact, except for the information derived from the few EPD which entered the prospective controlled trial the Children's Cancer Study Group initiated in the middle 1970s, essentially for medulloblastoma [1] and while waiting for the definitive results of the first cooperative trial exclusively designed for childhood EPD, conducted by the Paediatric Oncology Group in these present years, we have to acknowledge that most of what we know about these tumours derives from retrospective studies like the present one or by large single institutional series.

The patients of our series enjoyed a 10-year OS and PFS of 55.5% (CI 41.4–69.4%) and 35% (CI 21.4–47.8%), respectively (Fig. 1). These survival data compare favourably with other recent reports, which report 5-year OS and PFS varying from 56% to 44% and from 38% to 47% [5–8, 10–15]. These data emphasise the fact that the prognosis of children affected by these tumours is poor to fair at best, and unlike the progress made in the therapy of other childhood malignancies, it appears that the outlook for these patients has not improved in the last few decades.

We approached this cohort of patients wondering if, within them, different prognostic groups exist, based on clinical characteristics such as patient's age, tumour site, histology, tumour resection, use of RT and CT.

Radical resection emerged as a statistically significant prognostic factor capable of predicting a favourable long-term outcome. In fact, the children who had the tumour macroscopically resected enjoyed a survival which almost doubled the one of those for whom it was possible, at the very most, to perform only a partial resection. This is in line with what was reported for other malignant CNS tumours such medulloblastoma and childhood high grade glioma [9]. We used both neurosurgical and neuroradiological criteria to judge the entity of the surgical act. It is believed that only combining those two criteria that a favourable prognostic group, based on surgery, can be identified. Most likely the introduction of MRI in the daily management of children with brain tumours, the adoption of more strict criteria in judging surgery and the use of a more appropriate timing for performing postsurgical contrast-enhanced studies (within 72 hours from surgery) will help in defining more precisely this cohort of patients. In fact, if in the literature there is not a full agreement among studies on the prognostic relevance on the surgical act, this probably should be related to the fact that the methods (CAT scan vs. MRI), the timing of performing those tests and the criteria for defining complete surgical resection vary greatly between trials [7,6,10–15]. Any future prospective study should weigh carefully the influence of all these variables in patient stratification and on the possibility of producing reproducible and comparable data.

In the present series, about 60% of the children had the tumour completely resected, regardless of primary tu-

TABLE III. Univariate Analysis of Some Patients' Clinical Characteristics

Clinical characteristic	No. pts.	10 years OS[a] (%)	Log rank *p*-value	10 years PFS[a] (%)	Log rank *p* value
Age (years)					
< = 5	45	41.9	0.03	19.9	0.008
>5	47	68.7		51.2	
Sex					
female	40	47.1	0.15	31.9	0.6
male	52	61.2		36.9	
Site					
infratentorial	60	47.2	0.46	33.9	0.7
supratentorial	32	66.8		37.7	
Histology					
non-malignant/non-anaplastic	61	60.0	0.18	45.04	0.04
malignant/anaplastic	31	44.5		0[b]	
Surgery					
complete resection	53	69.8	0.01	57.2	0.0001
incomplete resection	35	32.5		11.1	
Radiotherapy					
yes	74	58.4	0.015	38.2	0.0096
no	16	52.0		20.4	
Chemotherapy					
yes	37	46.5	0.4	24.02	0.17
no	48	62.5		45.6	
Radiotherapy field					
regional/local	40	56.4	0.79	32.3	0.6
craniospinal	37	55.4		32.1	

[a]OS, overall survival; PFS, progression-free survival.
[b]Referred to 5 years OS and PFS (see text for comments).

mour site and histology. In the literature the complete resection rate varies between 13% and 56% [5,6,7,10, 12,15]. It could well be that in our studies there was an overestimation of the complete resection rate. Nevertheless, this potential bias does not weaken the relevance of the data. For this analysis, it was impossible to further categorise the group of patients who had less than a complete resection according to the amount of the post surgical residual (e.g., biopsy vs. partial resection). Therefore, it remains to be demonstrated if in case of macroscopical tumour residual, its amount has some prognostic implication. If the trend is in favour of a maximum radical resection whenever possible, one should temper the attitude of radically removing EPD considering the risk of such radical intervention. For example, infratentorial EPD quite often tend to grow along the cerebellar-pontine angle in intimate relationship with cranial nerves, and/or inferiorly toward the upper part of the cervical spine. In these cases, attempts at radical removal can be associated with severe morbidity [6,10]. Finally, one should also consider the possibility that the resectability of an EPD may reflect, more than anything else, a favourable tumour biology which determines a growth pattern amenable to radical removal.

For this cohort of patients, when RT was introduced in a multivariate analysis, it reached a marginal statistical significance value only for the PFS and not for the OS. Thus, considering also that some sort of patient selection for recommending RT may have biased the present analysis, this series failed to document a clear impact of the use of RT on the outcome of children affected by EPD. Among the different publications which specifically addressed the issue of prognostic factor analyses for childhood EPD in retrospective single institution or cooperative studies [6–8,10–13], only the series produced by Rousseau et al. [5] indicated the relevant prognostic impact of RT on the survival of children with this rare childhood neoplasm. Thus, at the present standard of knowledge on this tumour, it seems that the most striking evidence in favour of the role of postsurgical RT in the outcome of these patients, derives from the reasonable consideration that modern multidisciplinary approaches, based also on the use of RT, are behind the progresses in survival observed between the first pure surgical series of the 1930s and 1940s, reporting survival in the 15% to 30% range [16,17], and the more recent ones, with survival rate over 40% [5–8,10–15,18,19]. Who writes believes that despite the fact that the use of RT in the treatment of childhood EPD has never been supported by the results of prospective randomised clinical trials or by consistent statistical data, the present standard of care for this childhood CNS neoplasm is represented by the therapeutic sequence, surgery and radiotherapy. It will be left to future clinical trials to identify possible subgroups of

EPD which may be treated according to therapeutic strategies not inclusive of RT as some Authors have suggested [20,21]. Furthermore, the present standard of care must be improved to increase the local tumour control rate particularly in case of gross surgical tumour residuals.

The present analysis could not really address the long-lasting issue of which field of RT should be used for treating this neoplasm [22,23]. We entered also the field of RT regional/local vs. craniospinal, in the univariate analysis of the prognostic factors of this group of children and no difference emerged in term of OS and PFS between the two groups. However, once again, the possible selection process of patients treated with one modality or the other, the nonhomogeneous staging procedures and treatment modalities used for this cohort of children, do not allow us to draw any pertinent conclusions. However, in this context, assuming the limitation of our analysis, we reflect the concern raised by more specifically designed studies, regarding the real need for prophylactic neuroaxis irradiation in case of non-metastatic EPD at diagnosis [14,15,22–25]. Finally, considering that all patients but four received doses over 45 Gy, no dose analysis could be performed.

When entered in multivariate analyses, none of the other clinical characteristics we studied were statistically significant in predicting long-term survival. It could be said that this is also not in contrast with the pertinent literature so far published. In fact, except for surgery and maybe RT, no other clinical characteristic is consistently reported to be predictive of long-term survival for childhood EPD. In our series, also histology, despite resulted significant only for PFS, loses the statistical relevance when entered in the multivariate analysis. Risk categories based on histology have been proposed by many authors; however, it is interesting to note that none of them shared the same criteria for identifying those histological groups [8,14,15,26]. It is expected that variables like tumour ploidy or presence of genetic abnormalities may emerge as more reliable factors for defining risk categories than morphology.

CONCLUSION

This retrospective review of a large number of children with EPD adds weight to the findings of others that suggest the importance of total surgical removal in the management of childhood EPD. Other factors we analysed, such as age, use of RT and histology, were not found to be significant. However, although our review includes one of the largest collection of children with EPD ever reported, it has the limitation to be expected when data are gathered from multiple institutions comprising 16 years of experience. Important pieces of information are missing and consideration of the methods of evaluating diagnosis and therapy is lacking. It is also clear that due to the rarity of this neoplasm, no single institution will be able to produce meaningful data in a reasonable time frame. Prognostic factors change with time as better treatments are devised and more accurate imaging and histopathological techniques evolve. These considerations call attention to the need for carefully designed cooperative clinical trials on EPD that include systemised therapies and centralised review of critical data. Only in this way can valid contemporary information be gathered concerning this rare but potentially devastating childhood CNS tumour.

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